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09/721,864	11/24/2000	David Scheinberg	D6126	4077

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/721,864	Applicant(s) SCHEINBERG ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- *The MAILING DATE of this communication appears n the cover sheet with the correspondenc address* --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *8-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant election of group I, claims 1-7, 16-22, species a tumor greater than 1 mm in size, an antibody or fragment thereof, and bismuth-213, without traverse in paper No: 5 of 02/04/02 is acknowledged.

Accordingly, claims 1-7, species a tumor greater than 1 mm in size, an antibody or fragment thereof, and bismuth 213 are examined in the instant application. Claims 16-22 are withdrawn from consideration as being drawn to non-elected species.

OBJECTION

Claim 6 is objected to because multiply is a verb, which cannot follow another verb.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, SCOPE

1. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing tumors of 3-5 mm in diameter in size, comprising administering a construct comprising an antibody specific to said tumor, wherein said antibody is labeled with an alpha emitting isotope, does not reasonably provide enablement for a method of killing a tumor greater than 1 mm in size, comprising administering a "construct" comprising an alpha emitting isotope, wherein said construct is an antibody or a fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-7 are drawn to a method of killing a tumor greater than 1 mm in size, comprising administering a "construct" comprising an alpha emitting isotope, wherein said construct is an antibody or a fragment thereof.

Claims 1-7 encompass a method of killing a tumor greater than 1 mm in size, comprising administering any construct or any antibody or fragment thereof comprising an alpha emitting isotope.

It is noted that not any construct or any antibody is specically targeted to tumors. For example, a construct, such as a DNA vector, or a peptide, which do not have the ability of targeting to the tumors, or an antibody which could be targeted to a healthy organ, such as the heart, and not to the tumors. Thus one of skill in the art would not have expected that any construct or any antibody labeled with an alpha emitting isotope would be effective in selectively killing tumors.

Further, a construct which encompasses any compound, and not just an antibody or a cytokine or a receptor ligand, e.g. a piece of metal, would not have a required half-life, nor any antibody fragment would be effective in treating tumors when labeled with Bi-213. Adams GP et al, 2000, Nuclear Med Biol, 27: 339-346, teach that single chain Fv and diabody, which are known for their short-lives, are not effective in selectively killing tumors when coupled with Bi-213. Adams et al further teach that more effort must be expanded to match the physical half-lives of therapeutic isotopes with the biological properties of their delivery vehicles, and that the best use of the short-lived Bi-213 may be in antibody targeting where the isotope complexes have elimination half-lives on the order of 30 min (p.345, first column, second paragraph).

In view of the above, it would have been undue experimentation to practice the claimed invention as broadly as claimed.

2. Claims 4, 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing tumors of 3-5 mm in diameter in size, comprising administering a construct comprising an antibody specific to said tumor, wherein said antibody is labeled with an alpha emitting isotope, and wherein said alpha emitting isotope has a specific activity of 30 mCi/mg, as disclosed in the specification and at a dosage of 150-200 uCi per mouse as disclosed by Hartman et al, 1994, Cancer Res, 54: 4362-70, does not reasonably provide enablement for a method of killing a tumor greater than 1 mm in size, comprising administering a construct comprising an alpha emitting isotope, wherein said alpha emitting isotope has a specific activity of from about 0.05 mCi/mg to about 100 mCi/mg, and is administered at a dose of about 0.1 mg/m^2 to about 50 mg/m^2 The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 4, 7 are drawn to a method of killing a tumor greater than 1 mm in size, comprising administering a construct comprising an alpha emitting isotope, wherein said alpha emitting isotope has a specific activity of from about 0.05 mCi/mg to about 100 mCi/mg, and is administered at a dose of about 0.1 mg/m^2 to about 50 mg/m^2.

The specification discloses that at a specific activity of B-212 at 0.2 mCi/mg, it is unlikely that specific cell killing occurs (p. 40, last paragraph). Since 0.2 mCi/mg is

significantly higher than 0.05 mCi/mg, one would expect that at a specific activity of B-212 at 0.05 mCi/mg, it is unlikely that specific cell killing occurs

The specification also discloses that efficiency of labeling with Bi-213 decreases in direct relationship to the specific activity desired and that labeling efficiency is at 50-70% with specific activity of 50 mCi/mg (p.34, last paragraph). The specification however does not disclose how to make an alpha emitting isotope with specific activity at about 100 mCi/mg. Since efficiency of labeling with Bi-213 decreases in direct relationship to the specific activity desired, it is unpredictable that a specific activity at about 100 mCi/mg could be achieved with any practical efficiency.

Further, at a dose of 50 mg/m^2 and a specific activity of about 100 mCi/mg, one would expect an amount of 5,000 mCi/m^2 is administered. Adams et al, *supra*, teach that for mice, a dose of 1100 uCi and 600 uCi are completely lethal (. 341, first column, under Therapy studies). Assuming a mouse is 10 cm long, injection into a mouse would cover 100mm x 100 mm or 10000 mm^2. Since 5,000mCi/m^2 is equivalent to 5uCi/mm^2, one would expect that 50000 uCi would be injected into the mouse. Thus one would expect that the claimed dosage is lethal and is not practical.

In view of the above, it would have been undue experimentation to practice the claimed invention as broadly as claimed.

3. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing tumors of 3-5 mm in diameter in size, comprising administering a construct comprising an antibody specific to said tumor, wherein said antibody is labeled with an alpha emitting isotope, does not

reasonably provide enablement for a method of killing a tumor greater than "1 mm in size", comprising administering a construct comprising an alpha emitting isotope, wherein said construct is an antibody or a fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-7 are drawn to a method of killing a tumor greater than 1 mm in size, comprising administering a construct comprising an alpha emitting isotope, wherein said construct is an antibody or a fragment thereof.

Claims 1-7 encompass a method of killing a tumor of any size, provided that it is greater than 1 mm in size, comprising administering a construct comprising an alpha emitting isotope, wherein said construct is an antibody or a fragment thereof.

The specification discloses that tumors of 3-5 mm diameter in size are treated with Bi-213 or Bi-212 labeled antibodies (p.43). Thus the maximum volume of the disclosed treated tumors is 5mm x 5mm x 3.14/6 or $13mm^3$.

Horak, E et al, December 1997, J nuclear med, 38(12): 1944-50 teach that tumors having a volume of 15 mm^3 could be treated with antibodies labeled with lead-212 (p.1948, second column, second paragraph) . Horak et al further teach that large tumors having a volume of 146 mm^3 could not be treated with said antibodies. Similarly, Hartman, F et al, 1994, Cancer Res, 54: 4362-70, teach that large tumor having a volume of 936 mm^3 could not be treated with antibodies labeled with Bi-212 (p.4367, first column, first paragraph).

Thus one would have expected that a tumor of any size, provided it is greater than 1 mm could be treated, in view of the teaching of Horak et al and Hartman et al

In view of the above, it would have been undue experimentation to practice the claimed invention as broadly as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by Horak, E, December 1997, J nuclear med, 38(12): 1944-50.

Claims 1-4 are drawn to a method of killing a tumor greater than 1 mm in size, comprising administering a construct comprising an alpha emitting isotope, wherein said construct is an antibody, and wherein said alpha emitting isotope is lead-212 and wherein said alpha emitting isotope has a specific activity from about 0.05 mCi/mg to about 100 mCi/mg.

Due to the indefinite language of claim 1 and for the purpose of compact prosecution it is assumed that claims 1-4 are drawn to a method of killing a tumor

greater than 1 mm in diameter in size. Thus the volume of the disclosed treated tumors is at least 1mm x 1mm x 3.14/6 or 0.52 mm^3.

Horak, E et al teach that tumors having a volume of 15 mm^3 could be treated with antibodies labeled with lead-212, having a specific activity of 0.6 to 1.5 uCi/ug (p.1946, first column, and p.1948, second column, second paragraph).

Since 0.6 to 1.5 uCi/ug is the same as 0.6 to 1.5 mCi/mg, the specific activity of the labeled antibody taught by Horak et al is within the range of the claimed specific activity. Further, tumors having a volume of 15 mm^3 taught by Horak et al are inherently at least 1 mm in size. Thus the method taught by Horak et al is the same as the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over obvious over Horak et al, *supra*, in view of Hartman et al, *supra*, Kasperson, FM et al, 1995, Nuclear Med Comm, 16: 468-476, and US PN=4,665,897.

Claims 1-7 are drawn to a method of killing a tumor greater than 1 mm in size, comprising administering a construct comprising an alpha emitting isotope, wherein said construct is an antibody, and said alpha emitting isotope is bismuth-213, and wherein

said alpha emitting isotope has a specific activity from about 0.05 mCi/mg to about 100 mCi/mg, and is administered at a dose of about 0.1 mg/m^2 to about 50 mg/m^2. Said alpha emitting isotope is administered in a dose adequate to deliver a minimum of 1 alpha track per cell. Said construct is multiply administered.

Due to the indefinite language of claim 1 and for the purpose of compact prosecution it is assumed that claims 1-4 are drawn to a method of killing a tumor greater than 1 mm in diameter in size. Thus the volume of the disclosed treated tumors is at least 1mm x 1mm x 3.14/6 or 0.52 mm^3.

Horak, E et al teach that tumors having a volume of 15 mm^3 could be treated with antibodies labeled with lead-212, having a specific activity of 0.6 to 1.5 uCi/ug (p.1946, first column, and p.1948, second column, second paragraph).

Thus the tumors taught by Horak et al are at least 1 mm in size. Further, since 0.6 to 1.5 uCi/ug is the same as 0.6 to 1.5 mCi/mg, the specific activity of the labeled antibody taught by Horak et al is within the range of the claimed specific activity.

drop - Horak, E et al do not teach that the antibodies are labeled with Bi-213, and are administered at a dose of about 0.1 mg/m^2 to about 50 mg/m^2 or at a dose adequate to deliver a minimum of 1 alpha track per cell. Horak, E et al do not teach that the labeled antibodies are multiply administered.

Hartman et al teach that except bulky tumors of a size of 936 mm^3, small tumors could be treated with antibodies labeled with B-212.

Kaspersen et al teach that Bi-213 can be an alternative to Bi-212, with the advantage of safer and easier production (p.475, first column, first paragraph).

PN=4,665,897 teach a method of treating tumors comprising administering antibodies containing inactive nuclide that could be rendered radioactive with externally generated radiation, wherein the steps of said method are repeated as many times as necessary to effect remission or destruction of tumors (Claims 28, 35, 36). Said radiation includes alpha particles (claim 27).

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to treat tumors of at least 1 mm in size using the method of Horak et al or Hartman et al, comprising administering an antibody labeled with lead-212 or Bi-212. It would have been obvious to substitute lead-212 or Bi-212 with Bi-213, because Bi-213 has the advantage of safer and easier production, as taught by Kasperson et al. It would have been obvious to administer the labeled antibody repeatly, as taught by PN=4,665,897, to ensure destruction of the tumors. With regards to the dosage of the labeled antibodies recited in claims 5, 7, to determine optimum dosage is within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425. One of ordinary skill in the art would have been motivated to treat tumors having at least 1mm in size using antibodies labeled with Bi-213 with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

May 3, 2002